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Prediction of Poor Mobilization of Autologous CD34+ Cells with Growth Factor in Multiple Myeloma Patients: Implications for Risk-Stratification

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It is unknown whether clinical characteristics can successfully predict which multiple myeloma (MM) patients would be poor mobilizers with growth factor (GF) alone so they can be assigned to mobilization with chemotherapy + GF or GF + plerixafor. MM patients (N = 477) who underwent autologous mobilization with GF were retrospectively reviewed and assigned into training and validation cohorts. In multiple regression analysis, age, platelet count at time of mobilization, type of GF utilized, and extent of exposure to lenalidomide independently correlated with peripheral blood (PB)-CD34+ and were integrated in a predicting score (PS) for poor mobilizers, defined as PB-CD34+ < 20/mm^3 4 days after initiation of GF. There was no correlation between institution, gender, time between diagnosis, and mobilization or plasma cells in the bone marrow at time of mobilization and PBCD34+. The PS cut-off found in the training cohort to have 90% sensitivity for prediction of poor mobilizers performed with 89.7% sensitivity but only 34.8% specificity in the validation cohort. Conversely, the PS cut-off developed to have 90% specificity performed with 86.9% specificity but only 37% sensitivity. We conclude that clinical characteristics identifiable before initiation of mobilization should not be used to stratify MM patients for different mobilization strategies.

INTRODUCTION

Autologous hematopoietic progenitor cell transplantation after high-dose chemotherapy is a common and effective treatment for patients with multiple myeloma (MM) [1-4]. This procedure requires the prior procurement and cryopreservation of hematopoietic progenitor cells to ensure safe engraftment [5].

The administration of hematopoietic growth factors (GFs), particularly granulocyte-colony stimulating factor (G-CSF) or granulocyte macrophage-colony stimulating factor, is the simplest method to mobilize hematopoietic progenitor cells (HPCs). GFs stimulate neutrophil production, maturation, and protease release, leading to disruption of the binding of CD34+ progenitor cells from the bone marrow stroma and its consequent migration to the peripheral blood [6]. The most important interaction disrupted is the 1 between the receptor CXCR4 (present in CD34+ cells) and its ligand, CXCL12 or stromal-derived growth factor−1 [7].

Two other strategies are known to increase the CD34+ yield and reduce mobilization failure when compared with GF-alone mobilization. The administration of chemotherapy, particularly high-dose cyclophosphamide followed by daily GF, improves CD34+ yield but is associated with higher risk of complications, particularly fever and neutropenia [8,9]. More recently, the combination of G-CSF and plerixafor, an inhibitor of CXCR4 that prevents its binding to stromal-derived growth factor−1, has been shown to reduce the risk of mobilization failure and increase CD34+ yield [10]. Plerixafor has a favorable side effect profile but a high cost, making it not cost effective on a substantial proportion of patients who would mobilize properly with GF alone.

Considering the caveats of each mobilization strategy, it would be of great value to risk stratify patients in regards to their risk of "poor mobilization" with GF alone so they can proceed with chemotherapy + GF or GF + plerixafor mobilization. In the present study, we utilized a large cohort of MM patients undergoing first mobilization with GF to develop a predictive model for poor mobilization and tested the operational characteristics of this model in an independent but similar cohort.

MATERIALS AND METHODS

This is a retrospective study utilizing data on consecutive patients with MM who underwent first autologous HPC mobilization at the Mayo Clinic, Rochester, Minnesota (Mayo) or at the Medical University of South Carolina, Charleston, South Carolina (MUSC) utilizing primarily GF, between 2000 and early 2013. Information of interest included gender, age, duration of prior therapy with specific myeloma drugs, percentage of plasma cells in the bone marrow before mobilization (within a month and with no subsequent antimyeloma therapy), platelet count before mobilization, time between diagnosis and mobilization, and number of CD34+ cells in the peripheral blood (PB-CD34+) on the fourth day after initiation of administration of GF. The majority of patients were managed elsewhere before being referred to our institutions for transplantation. Relevant information on prior use of radiation was not consistently captured and verified and, therefore, not available for the majority of patients in our mobilization databases. The vast majority of patients received filgrastim as mobilizing GF at the dose of 10 μg/kg/day, with the exception of 84 patients from MUSC who received pegfilgrastim 12 mg as previously reported [11]. Only patients with complete dataset were included in the analysis. This study was approved by both Mayo and MUSC institutional review boards.

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Table 1
Characteristics of Multiple Myeloma Patients in the Training and Validation Cohorts

Characteristic	Training Cohort	Validation Cohort	All Patients
	n = 239	n = 238	N = 477
Institution			
Mayo	173 (72.4%)	173 (72.7%)	346 (72.6%)
MUSC	66 (27.6%)	65 (27.3%)	131 (27.4%)
Age, yr*	59.5 (52.8-65.5)	59.4 (52.5-65.3)	59.4 (52.7-65.4)
Male gender	140 (58.6%)	124 (52.1%)	264 (55.3%)
Patients with prior lenalidomide therapy	63 (26.4%)	71 (29.8%)	134 (28.1%)
Plasma cells in bone marrow, %*	6 (2.5-15)	5 (3-15)	5 (3-15)
Platelet count before mobilization*	222 (183.5-277.5)	223 (181.2-285.7)	223 (182-281)
Interval from diagnosis to mobilization, mo*	5.9 (4.8-8.1)	6.1 (4.8-8.7)	6 (4.8-8.5)
Growth factor			
Filgrastim	197 (82.4%)	196 (82.3%)	393 (82.4%)
Pegfilgrastim	42 (17.5%)	42 (17.6%)	84 (17.6%)
PB-CD34+*	17 (7-30)	16 (9-25)	16 (8-28)
PB-CD34+			
$<10/mm^3$	72 (30.1%)	65 (27.3%)	137 (28.7%)
$<20/mm^3$	136 (56.9%)	146 (61.3%)	282 (59.1%)

Data presented are n (%) unless otherwise indicated.
* Median (interquartile range).

Definition of Poor Mobilization

There is no consensus in the literature on which patients should be considered poor mobilizers. Here we utilized an operational definition of poor mobilization as the failure to obtain a PB-CD34+ count in PB after 4 days of initiation of GF of 20 cells/mm^3 or higher. We adopted this definition because, contrary to CD34+ daily apheresis yield or total CD34+ collection, PB-CD34+ is not dependent on other factors, such as performance and parameters of the apheresis equipment, institutional practices (such as parameters to stop apheresis) or the use of plerixafor on or after day 4. In fact, many of the patients included in this analysis were treated under previously published algorithms for use of "just in time" plerixafor from both institutions [12,13]. Moreover, PB-CD34+ has been closely correlated with apheresis yield [12,14,15]. In a post hoc analysis of the phase III study comparing G-CSF with G-CSF + plerixafor, 46.5% of the patients receiving G-CSF alone had PB-CD34+ $<20/mm^3$ on day 4. Only 83.3% of these patients collected $\geq 2 \times 10^6$ CD34+/kg (minimum yield) and only 36.7% collected $\geq 6 \times 10^6$ CD34+/kg (optimal yield). These figures were respectively 98.6% and 73.9% among the 53.5% of MM patients with PB-CD34+ $\geq 20/mm^3$, reinforcing our choice of PB-CD34+ $<20/mm^3$ as our operational definition of poor mobilization [16].

Of interest, PB-CD34+ has been adopted in many institutions as a trigger for "just in time" use of plerixafor [12]. At Mayo, MM patients collecting cells for more than 1 transplantation procedure (target of 4×10^6 CD34+/kg) will receive plerixafor if PB-CD34+ $< 20/mm^3$ [13], whereas at MUSC, the target for those patients is 6×10^6 CD34+/kg, and they receive plerixafor if PBCD34+ $\leq 25/mm^3$ [12].

Development and Validation of Predictive Model

To obtain 2 comparable cohorts (training cohort and validation cohort), patients were randomly allocated in the 2 cohorts after stratification according to 2 factors known to strongly affect mobilization: age [17] and type of growth factor (filgrastim and pegfilgrastim) [11]. To account for any intrinsic difference between Mayo and MUSC, cases were also stratified by institution of origin.

In the training cohort, we investigated the contribution of the independent variables (age, gender, duration of prior exposure to specific myeloma drugs, percentage of plasma cells in the bone marrow before mobilization, platelet count before mobilization, time from diagnosis to mobilization, type of growth factor utilized, and institution of origin) in influencing the dependent variable, PB-CD34+, utilizing multiple regression analysis to determine the best fit predictive model.

Patients were classified as poor mobilizers (actual PB-CD34+ $< 20/mm^3$) or good mobilizers (actual PB-CD34+ $\geq 20/mm^3$). We utilized the results of the multiple regression analysis to generate a predicting score (PS) for each patient (with lower PS indicating higher risk of poor mobilization). We subsequently built receiving operator characteristics (ROC) curves, determining the sensitivity and specificity of different cut-offs of the PS to identify patients destined to be poor mobilizers in the training cohorts. The cut-offs corresponding to the performance parameters of interest (80% sensitivity, 90% sensitivity, 80% specificity, and 90% specificity) where then applied to the validation cohort.

Because some institutions will consider adequate a GF mobilization producing a PB-CD34+ of 10 cells/mm^3 or greater, we also performed an exploratory analysis repeating the steps above but defining as poor mobilizers the patients with PB-CD34+ $< 10/mm^3$.

Statistics

Categorical variables are described in terms of percentage, whereas continuous variables are described in terms of median and interquartile range. Simple regression was utilized to establish correlations between each of the independent variables and PB-CD34+. The development of the predictive equation utilized multiple regression with stepwise forward inclusion of independent variables. Comparison of continuous variables between groups was performed utilizing Mann-Whitney U test. All statistic analysis

Table 2
Clinical Variables Associated with PB-CD34+ in the Training Cohort

	Univariate Linear Regression			Multiple Regression		
	Beta	95% CI	*P*	Beta	95% CI	*P*
Age (per year)	−.370	−.577 to −.162	<.001	−.352	−.629 to .074	.013
Gender (male)	.990	−2.892 to 4.872	.62			
Duration of prior lenalidomide therapy	−1.396	−2.167 to -.625	<.001	−1.80	−2.96 to −.64	.003
% PC in the bone marrow	−.112	−.257 to .033	.13			
Platelet count (per 1,000/mm^3)	.066	.045 to .087	<.001	.066	.034 to .099	<.001
Interval from diagnosis to mobilization (per month)	−.050	−.158 to .059	.37			
Growth factor*	11.981	7.029 to 16.932	<.001	9.72	3.06 to 16.38	.004
Institution†	−4.570	−10.665 to 1.525	.141			

CI indicates confidence interval; PC, plasma cells.
* Pegfilgrastim versus filgrastim.
† Mayo versus MUSC.

was performed using SPSS (IBM Corp. Released 2010. IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY). In all inference analyses, 2-sided *P* values of less than .05 were considered to indicate statistical significance.

RESULTS

Patient Characteristics

During the periods of interest covered in this study, 606 patients with MM underwent autologous HPC mobilization with GF among the 2 institutions. Of those, 477 (78.7%) met eligibility criteria, were included in the analysis, and randomly assigned to the training cohort (n = 239) or validation cohort (n = 238). The age range was 21 to 75 years in the training cohort and 29 to 74 years in the validation cohort. Patients from Mayo and MUSC were comparable, except for MUSC patients being mobilized in more recent years and have greater exposure to lenalidomide. As displayed in Table 1, training and validation cohorts were comparable in all relevant aspects.

Predictors of Poor Mobilization

As described in methods, we utilized multiple regression to determine the factors independently influencing PB-CD34+ and to determine the PS based on those factors (best fit model). We observed that age and duration of prior exposure to lenalidomide (but not exposure to cyclophosphamide, bortezomib or thalidomide) correlated negatively, although platelet count at time of mobilization and use of pegfilgrastim instead of filgrastim correlated positively with PB-CD34+. There was no correlation between institution

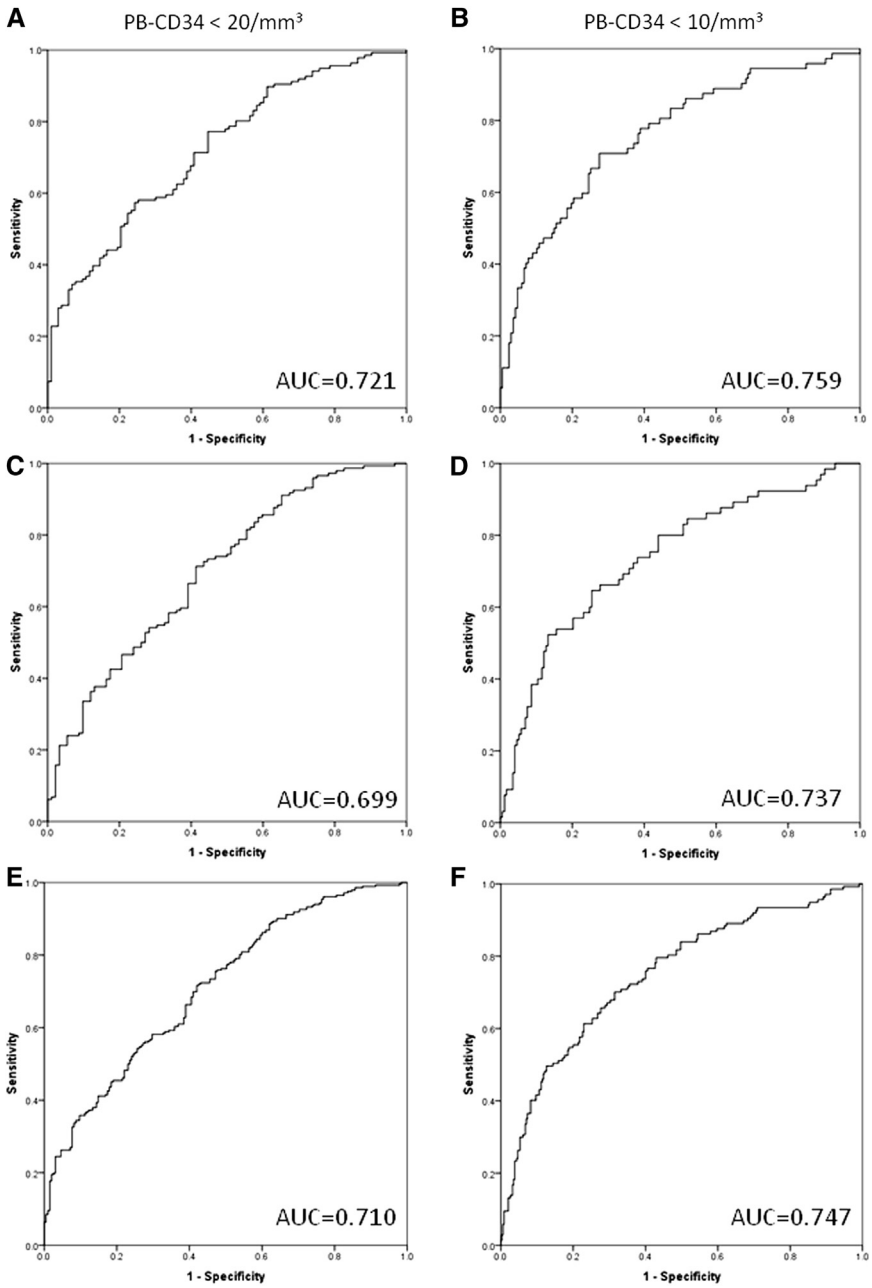

Figure 1. Receiver operating characteristic (ROC) displaying the performance of different cut-offs of the predicting score (PS) in the training cohort (A and B), validation cohort (C and D) and both cohorts combined (E and F).

(Mayo or MUSC), gender, time between diagnosis and mobilization, percentage of plasma cells in the bone marrow at time of mobilization, and PBCD34+ (Table 2). From the multiple regression model, the equation that best predicts for PB-CD34+ is:

Predictive score (PS) = .066 × platelets (10^3/mm^3) + 9.721 × GF (GF = 0 if filgrastim, 1 if pegfilgrastim) −1.801 × duration of lenalidomide exposure (in months) −.352 × age + 28.254.

There were 136 (56.9%) patients in the training cohort who were classified as poor mobilizers with PB-CD34+ < 20/mm^3 and 72 (30.1%) were poor mobilizers under the PB-CD34+ < 10/mm^3 alternative definition. Figure 1 display the ROCs for the training cohort. Utilizing the PB-CD34+ < 20/mm^3 definition of poor mobilizer, a PS of 29.7 was the cut-off for 90% sensitivity and a PS of 17.4 was the cut-off for 90% specificity. For the PB-CD34+ < 10/mm^3 definition of poor mobilizer, the cut-offs were 27.6 and 15.6 for 90% sensitivity and 90% specificity respectively.

Validation

Overall 146 patients (61.6%) in the validation cohort were poor mobilizers utilizing the PB-CD34+ < 20/mm^3 definition, whereas 65 (27.4%) were poor mobilizers when the PB-CD34+ < 10/mm^3 alternative definition was used. When PS distribution is displayed for actual poor mobilizers and good mobilizers, it becomes evident that there is great overlap between the 2 categories, despite the distribution being statistically different (Figure 2).

Table 3 displays the performance of the cut-off PS derived from the training cohort when applied to the validation cohort for optimal sensitivity and optimal specificity. It becomes clear that the use of premobilization clinical characteristics is inadequate to predict poor mobilization. The use of premobilization clinical characteristics to stratify patients to different mobilization strategies would lead to either excessive rate of poor mobilization or unnecessary use of mobilization alternatives (such as plerixafor) or both.

DISCUSSION

Although GF alone is the simplest and least expensive method to mobilize autologous CD34+ cells, it has unacceptable shortfalls, particularly lower yields, and higher rates of mobilization failure. Alternatives to GF-alone mobilization, namely GF + plerixafor or chemotherapy + GF, are more toxic, more expensive, and/or less convenient but will lead to better collections [8-10,18,19]. The identification of patients who are likely to have suboptimal collection with GF before beginning of mobilization would allow transplant physicians to assign them to an alternative strategy while proceeding with GF-alone mobilization for the remaining patients.

Several factors have been associated with poor mobilization in MM, including age, bone marrow involvement with the disease [20], prior lenalidomide therapy [21-23], prior therapy with melphalan [24-26], number of prior lines of therapy [24], and extensive irradiation to bone marrow sites [20,25]. However, no predictive system utilizing those risk factors has been validated and their performance in risk stratifying patients for difference mobilization strategies has not been tested.

In the present analysis, utilizing a large cohort of MM patients from 2 different institutions and treated with modern therapy, we identified age, duration of prior lenalidomide exposure, platelet count before mobilization, and type of growth factor utilized for mobilization as independent predictors of PB-CD34+. Of interest, interval between diagnosis and mobilization and percentage of plasma cells in the bone marrow before mobilization (a surrogate for response to therapy and disease burden) did not affect mobilization (Table 2).

At a time when alternative safe mobilization strategies are available, more important than having an adequate tool to predict poor mobilization with GF is to understand its operational characteristics and the implications of its use for risk stratification. Some institutions have adopted mobilization algorithms for the use of plerixafor based on risk stratification [27]. However, the accuracy of these predicting systems is unknown. The stratification of patients for different mobilization strategies based on an inaccurate prediction system may lead to excessive cost (too many "false-positives," patients identified as poor mobilizers but who would actually mobilize well) or excessive mobilization failure (too many "false negatives," identification of patients as good mobilizers, who actually mobilize poorly).

Our findings from a large and contemporary database utilizing proper methodology with independent training and validation cohort indicates that even a robust predictive model has poor performance. This indicates that mobilization performance on GF is only partially determined by clinical characteristics identifiable before initiation of

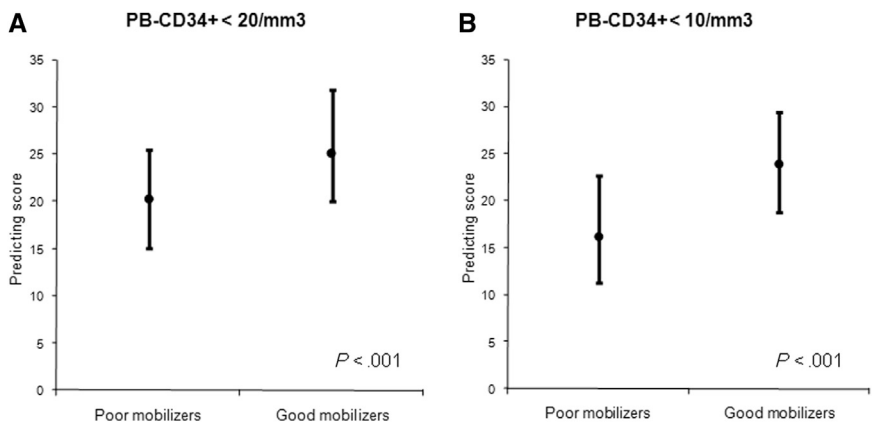

Figure 2. Distribution of the predicting score (PS) in patients from the validation cohort according to their classification as poor mobilizers (PM) or good mobilizers (GM). In (A) the definition of PM as PB-CD34+ < 20/mm^3 is used, whereas in (B) PM is defined as PB-CD34+ < 10/mm^3. Error bars represent median and interquartile range.

Table 3
Implications of Using the Best Fit Model for Risk Stratification based on Clinical Variables and Assignment to Different Mobilization Strategies

Objective	PS Cut-off*	Sensitivity†	Specificity†	Implications†
Definition of Poor Mobilizer as PB-CD34+ $< 20/mm^3$				
To properly detect 80% of the PM prior to starting mobilization so an alternative mobilization strategy can be used	26.7	80.1%	44.6%	19.9% of the PM (or 12.2% of the population) will not be allocated to alternative mobilization strategy and will have mobilization failure or suboptimal collection. 55.4% of the GM (or 21.4% of the population) will be wrongfully predicted to be PM and will receive unnecessary alternative mobilization strategy.
To properly detect 90% of the PM prior to starting mobilization so an alternative mobilization strategy can be used	29.7	89.7%	34.8%	10.3% of the PM (or 6.3% of the population) will not be allocated to alternative mobilization strategy and will have mobilization failure or suboptimal collection. 65.2% of the GM (or 25.2% of the population) will be wrongfully predicted to be PM and will receive unnecessary alternative mobilization strategy.
To properly detect 80% of the GM so they can be spared the toxicity and cost of an alternative mobilization strategy	19.8	47.3%	76.1%	52.7% of the PM (or 32.3% of the population) will not be allocated to alternative mobilization strategy and will have mobilization failure or suboptimal collection.23.9% of the GM (or 9.2% of the population) will be wrongfully predicted to be PM and will receive unnecessary alternative mobilization strategy.
To properly detect 90% of the GM so they can be spared the toxicity and cost of an alternative mobilization strategy	17.4	37.0%	86.9%	63% of the PM (or 38.6% of the population) will not be allocated to alternative mobilization strategy and will have mobilization failure or suboptimal collection.13.1% of the GM (or 5.1% of the population) will be wrongfully predicted to be PM and will receive unnecessary alternative mobilization strategy
Definition of poor mobilizer as PB-CD34+ $< 10/mm^3$				
To properly detect 80% of the PM prior to starting mobilization so an alternative mobilization strategy can be used	23.9	80%	52%	20% of the PM (or 5.5% of the population) will not be allocated to alternative mobilization strategy and will have mobilization failure or suboptimal collection. 48% of the GM (or 34.9% of the population) will be wrongfully predicted to be PM and will receive unnecessary alternative mobilization strategy.
To properly detect 90% of the PM prior to starting mobilization so an alternative mobilization strategy can be used	27.6	89.2%	32.4%	10.8% of the PM (or 2.9% of the population) will not be allocated to alternative mobilization strategy and will have mobilization failure or suboptimal collection. 67.6% of the GM (or 49.1% of the population) will be wrongfully predicted to be PM and will receive unnecessary alternative mobilization strategy.
To properly detect 80% of the GM so they can be spared the toxicity and cost of an alternative mobilization strategy	18.9	63.1%	74.6%	36.9% of the PM (or 10% of the population) will not be allocated to alternative mobilization strategy and will have mobilization failure or suboptimal collection.25.4% of the GM (or 18.5% of the population) will be wrongfully predicted to be PM and will receive unnecessary alternative mobilization strategy.
To properly detect 90% of the GM so they can be spared the toxicity and cost of an alternative mobilization strategy	15.6	43.1%	87.9%	56.9% of the PM (or 15.5% of the population) will not be allocated to alternative mobilization strategy and will have mobilization failure or suboptimal collection.12.1% of the GM (or 8.7% of the population) will be wrongfully predicted to be PM and will receive unnecessary alternative mobilization strategy

PS indicates predictive score; PM, poor mobilizers; GM, good mobilizers.

* PS as derived from the training cohort.

† Performance in the validation cohort.

mobilization. In fact, utilizing the PS to identify 90% of poor mobilizers before initiation of mobilization so they can be assigned to another mobilization strategy (eg, planned plerixafor or chemotherapy mobilization) would have resulted in over treatment of 25.2%, although still having poor mobilization in 6.3% of the patients (Table 3). It is important to emphasize that even though we believe our findings clearly indicate the limitations of using clinical characteristics to predict mobilization failure, variations in CD34+ enumeration likely also affected the results.

The above findings provide support to the strategy of "just in time" use of plerixafor based on PB-CD34+ enumeration over any strategy based on clinical characteristics. With "just in time" approach, patients receive steady state mobilization with growth factor only. After 4 or 5 days, patients reaching a prespecified PB-CD34+ count proceed to collection whereas patients with PB-CD34+ count inferior to the prespecified threshold have plerixafor added to their mobilization regimen and proceed to collection in the following day. Strategies for "just in time" plerixafor as published by the Mayo Clinic group [13], MUSC group [12], and others [28-30] do not rely on prediction by clinical characteristics and ensure that plerixafor is only utilized for patients who are actual poor mobilizers and likely to have inadequate collection (approximately 40% to 60% of patients). This approach keeps the rate of poor mobilization at $< 5\%$ and the rate of mobilization failure close to 0%. The limitations of predictive systems for poor mobilization and the advantage of "just in time" approaches have been acknowledged in a recently published consensus paper in autologous mobilization [31].

In summary, clinical characteristics identifiable before initiating mobilization are inadequate predictors of poor mobilization and should not be used to stratify multiple myeloma patients for different mobilization strategies. "Just-in-time" plerixafor is an attractive alternative to risk stratification.

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